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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
KENEDY, ANDREW A	

ART UNIT	PAPER NUMBER
1631	

DATE MAILED: 02/18/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/926,724	KITANO ET AL.	
	Examiner	Art Unit	
	Andrew A. Kenedy	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *7 December 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claim Rejections - 35 USC § 112

Claims 1-6 invoke 35 U.S.C. 112, sixth paragraph, but fail to comply with the requirement for setting forth adequate disclosure that shows what is meant by the means (or step)-plus-function language used.

Applicants have invoked 35 U.S.C. 112, sixth paragraph, through the use of the phrases "step for" and "means for" in Claims 1 and 4 respectively, wherein these phrases are followed by functional language and are not modified by sufficient structure, material, or acts for achieving the specified function. Applicants have failed to clearly indicate within the specification, the corresponding acts and structures that correspond to each "step for" and "means for" limitation of the claims. If applicants intend for their claims to be interpreted under 35 U.S.C. 112, sixth paragraph, then applicants are required to make the record clear by doing the following: 1) show why the claim language properly invokes 35 U.S.C. 112, sixth paragraph, 2) identify the function of each "step for" and "means for" phrase, and 3) identify the corresponding acts and structures within the specification, for each function.

Applicants must amend the specification to explicitly state what acts and structures correspond to each recited function, with reference to the claimed terms and phrases. Applicants are cautioned against adding new matter.

Claims 1-6 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 1 and 4 require providing a gene in step/means (a). Since applicants do not disclose where to obtain the gene, or what form the gene should take (i.e., chemical compound, DNA sequence data, or descriptive information such as name, function, and transcriptional level) one of ordinary skill in the art would not know how to provide the gene in a form that satisfies the applicants' method. It appears from the specification that applicants intend for general information about the gene to be provided, however, the claims are not limited to this. For example, while biological material is encompassed by the claim, the specification does not teach using biological material in the method.

Claims 1 and 4 require constructing a "calculation model" in step/means (b). No positive active steps are disclosed for constructing the model, and since no definition, formula or working example of the model is provided, one of ordinary skill in the art would not know how to construct a calculation model. Also in step/means (b), applicants require employing loci of the regulator binding sites or other factors that cause expression of the gene as parameters for the calculation model. Since applicants have not disclosed what the calculation model is, one of ordinary skill in the art would not know how to employ these parameters in the calculation

model. On pages 16-18 of the specification, applicants disclose that the parameters of the model include distance of the regulator binding site from the gene, size of the binding site, and binding affinity of the site, but fail to provide values for those parameters or disclose where numerical values for these parameters are readily obtained, other than through experimentation. As a result, it would require undue experimentation for one of ordinary skill in the art to practice applicants' invention.

Claims 1 and 4 require computing the level of transcription of the gene with respect to the constructed calculation model in step/means (c). Applicants have not disclosed a formula or the positive active steps for computing the level of transcription. One of ordinary skill in the art would not know how to compute the level of transcription with respect to the constructed calculation model without guidance since applicants have neither disclosed what the calculation model is or how it to apply it in computing a value for the level of transcription.

Claims 1 and 4 require obtaining empirically known expression of the gene by using parameter search algorithms to search parameters of the calculation model in step/means (d). Since empirically known expression is not a parameter of the model in step/means (b) – where parameters are stated as loci or other factors that cause expression of the gene – one of ordinary skill in the art would not know how to obtain empirically know expression of the gene by searching parameters of the model.

Claims 1 and 4 require predicting microstructures of an enhancer or promoter in step/means (e). Applicants have neither provided the positive active steps for predicting microstructures nor provided the necessary guidance or formulas for predicting microstructures. None of the preceding steps provide what is necessary for, or lead to, making a prediction of the microstructures of an enhancer or promoter. One of ordinary skill in the art would not know how to predict microstructures of an enhancer or promoter using the applicants' method without additional guidance, steps, or working examples.

Claims 1 and 4 state in the preamble that the goal is predicting the structure of a gene regulator binding site. However, applicants do not provide any step or means that achieves this goal. Without a positive active step or means to reach this goal, one of ordinary skill in the art would not be able to carry out the applicants' invention.

Claims 3 and 6 require making a prediction of microstructures based on whether the binding sites are dense or sparse. Applicants do not provide the necessary guidance or positive active steps required for making the determination of whether the binding sites are dense or sparse. If this determination were to be made by using a DNA sequence, which is within the skill in the art, then empirical determination of the physical positioning of the microstructures would be known as a result of having the actual sequence, and a prediction of the microstructure positioning would be a forgone conclusion, not requiring the applicants' prediction. Therefore, it appears that applicants did not intend for the user of the method to make the determination of whether binding sites are dense or sparse based on use of actual DNA sequence. In this case, one

of ordinary skill in the art would not know how to determine whether binding sites are dense or sparse without additional guidance or positive active steps.

With respect to Claims 1-6, applicants have not disclosed any working examples utilizing numerical values or otherwise, that demonstrate that the method as claimed is capable of predicting the structure of a gene regulator binding site.

Claims 1-6 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

With respect to Claim 1, the preamble goal is "a method for predicting the structure of a gene regulator binding site." It is unclear at which step of the method the structure of a gene regulator binding site is predicted. The final step listed, step (e), is a step for "predicting microstructures of the enhancer or promoter" which is not the same as the stated preamble goal of "predicting the structure of a gene regulator binding site." A "microstructure" is not necessarily the same thing as a "structure." And a "gene regulator binding site", which is an individual binding site for a transcription factor protein, is not identical to an "enhancer or promoter", which are regulatory loci of a gene. As such, the method steps are inconsistent with the preamble goal.

Claim 1 requires "predicting the structure of a gene regulator binding site." The phrase "the structure" is indefinite as to whether primary structure (DNA nucleotide sequence), secondary structure (in the case of DNA, the alpha helical form or abnormal forms thereof, such as hairpins, loops or triplex DNA), or tertiary structure (higher order structures involving protein-bound DNA that may be bent and/or folded, such as nucleosomal complexes) is to be predicted, thereby rendering the scope of the claim uncertain.

Claim 1 (a) requires "a step for providing a gene of interest." This phrase is indefinite as to what the source of the gene is, how it is obtained, and what the form of the gene takes (i.e., chemical compound, DNA sequence data, or descriptive information such as name, function, and transcriptional level), thereby rendering the scope of the claim uncertain.

Claim 1 (b) requires "a step for constructing a calculation model for each of the binding sites...employing, as parameters, loci of the regulator binding sites or other factors that cause expression of the gene." The phrase "a step for constructing" is indefinite since it gives no indication of the methodology to be used in constructing the calculation model or how the various parameters are to be incorporated into the model. The phrase "calculation model" is indefinite since it gives no indication of the particular mathematical expressions, algorithms, or methodology that constitute the model, and applicants do not disclose a technical definition or formula to indicate what the calculation model is. Further, it is unclear what characteristic(s) of the binding sites is to be modeled. The phrase "employing, as parameters, loci of the regulator binding sites" is unclear as to what properties of the loci are to be quantitated and used in

constructing the calculation model. The phrase "other factors that cause expression of the gene" is indefinite since it does not clearly describe the metes and bounds of what is encompassed, thereby rendering the scope of the claim uncertain.

Claim 1 (c) requires "a step for computing the level of transcription of the gene with respect to the above-constructed calculation model." The phrase "a step for computing" is indefinite because it does not specify the methodology used to compute the level of transcription, thereby rendering the scope of the claim uncertain. The phrase "with respect to the above-constructed calculation model" is unclear because it does not indicate how the "above-constructed calculation model" is to be used in computing the level of transcription.

Claim 1 (d) requires "a step for searching, through use of parameter search algorithms, parameters of the calculation model so that empirically known expression of the gene is obtained." The phrase "parameter search algorithms" is indefinite as to the particular search algorithms that are to be used, thereby rendering the scope of the invention uncertain. It is not clear whether the phrase "empirically known expression of the gene" is referring to temporal, spatial, or quantitative aspects of gene expression (such as "the level of transcription of the gene" concept used in Claim 1, step (c)). It is unclear how searching parameters of the calculation model would yield the "empirically known expression of the gene", since in step (b) the required parameters are indicated as being regulator binding site loci or other factors that cause gene expression, and a value for empirically known expression of a gene is not a parameter that would be present in either of those two categories.

Claim 1 (e) requires "a step for predicting microstructures of the enhancer or promoter." Although applicants give an example of what "microstructures" can be on page 10, paragraph 4 of the specification, the metes and bounds of what is encompassed by the term "microstructures" is unclear since applicants do not disclose a definition and since the term does not have an art understood meaning in the context of gene enhancers/promoters, thereby rendering the scope of the claim uncertain. The phrase "a step for predicting" is indefinite as to the methodology to used in making the prediction , thereby rendering the scope of the claim uncertain.

With respect to Claims 2 and 5, it appears that the terminology "%transcription per occurrence of transcription" does not have an art understood meaning. Further, it is unclear how the percentage of transcription (%transcription) that occurs could be classified as a factor that causes gene expression. Just the opposite, percentage of transcription (%transcription) would be the outcome of factors that cause gene expression.

With respect to Claims 3 and 6, the term "microstructures" is indefinite. The metes and bounds of what is encompassed by the term is unclear since applicants do not disclose a definition and since the term "microstructures" does not have an art understood meaning in the context of gene enhancers/promoters, thereby rendering the scope of the claims uncertain.

Claims 3 and 6 require knowing both the "portions where binding sites are dense" and the "portions where binding sites are sparse" within an enhancer or promoter. It is unclear how or

from where that knowledge is obtained. If that knowledge is to be obtained from a database of biological information, then it is unclear what database is to be used, and how and at which step that information is to be retrieved. If instead that knowledge is to be obtained directly from DNA sequencing followed by sequence analysis for the presence of binding site motifs, then it is unclear at what step this is to be performed. If instead that knowledge is part of the prediction obtained through the calculation model, then it is unclear what computational formula is used to make that determination and at which step in the method that computation is performed.

With respect to Claims 3 and 6, it is unclear what is meant by the phrase "they are physically remote from one another but interact with one another closely and functionally." Specifically, it is unclear whether the terminology "interact with one another closely" means that the distant microstructures come close together in terms of close physical proximity by looping or bending, or whether this terminology means the microstructures are simply interacting functionally in a coordinated manner (i.e., a cooperative interaction). Without a clear understanding of what is meant, one of ordinary skill in the art would not know what is required to meet the limitations of the claims.

Claim 4 is drawn to an "apparatus for predicting the structure of a gene regulator binding site" yet none of the means of the apparatus appear to output a prediction of the structure of a gene regulator site. For example, the means listed in Claim 4 (e) are for "predicting microstructures of the enhancer or promoter" which is not the same as the preamble goal of "predicting the structure of a gene regulator binding site." A "microstructure" is not necessarily

the same thing as a "structure." And a "gene regulator binding site", which is an individual binding site for a transcription factor protein, is not identical to an "enhancer or promoter", which are regulatory loci of a gene. Without requirement for a means that produces the prediction of the structure of a gene regulator binding site, the apparatus as claimed will not fulfill the goal of the preamble.

Claim 4 requires "predicting the structure of a gene regulator binding site." The phrase "the structure" is indefinite as to whether primary structure (DNA nucleotide sequence), secondary structure (in the case of DNA, the alpha helical form or abnormal forms thereof, such as hairpins, loops or triplex DNA), or tertiary structure (higher order structures involving protein-bound DNA that may be bent and/or folded, such as nucleosomal complexes) is to be predicted, thereby rendering the scope of the claim uncertain.

Claim 4 (a) requires "means for providing a gene of interest." This phrase is indefinite as to what the source of the gene is, how it is obtained, and what the form of the gene takes (for example, whether the gene takes the form of nucleotide sequence data, or whether the gene is provided as the actual DNA chemical compound), thereby rendering the scope of the claim uncertain.

Claim 4 (b) requires "means for constructing a calculation model which employs, as parameters, loci of the regulator binding sites within the enhancer or promoter region or other factors that cause expression of the gene." The phrase "calculation model" is indefinite since it

gives no indication of the particular mathematical expressions, algorithms, or methodology that constitute the model, and applicants do not disclose what the calculation model is, thereby rendering the means required to construct the model uncertain. Further, it is unclear what characteristic(s) of the binding sites is to be modeled. The phrase "employs, as parameters, loci of the regulator binding sites" is unclear as to what properties of the loci are to be quantitated and then used in constructing the calculation model. The phrase "other factors that cause expression of the gene" is indefinite since it does not clearly describe the metes and bounds of what is encompassed, thereby rendering the scope of the claim uncertain.

Claim 4 (c) requires "means for computing the level of transcription of the gene with respect to the above-constructed calculation model." The phrase "with respect to the above-constructed calculation model" is unclear because it does not indicate how the "above-constructed calculation model" is to be used in computing the level of transcription.

Claim 4 (d) requires "means for searching, through use of parameter search algorithms, parameters of the calculation model so that empirically known expression of the gene is obtained." The phrase "parameter search algorithms" is indefinite as to the particular search algorithms to be used, thereby rendering the scope of the invention uncertain. It is not clear whether the phrase "empirically known expression of the gene" is referring to temporal, spatial, or quantitative aspects of gene expression (such as "the level of transcription of the gene" concept used in Claim 1, step (c)). It is unclear how searching parameters of the calculation model would yield the "empirically known expression of the gene", since in Claim 4 (b) the

required parameters are indicated as being regulator binding site loci or other factors that cause gene expression, and a value for empirically known expression of a gene is not a parameter that fits into either of those categories.

Claim 4 (e) requires "means for predicting microstructures of the enhancer or promoter." Although applicants give an example of what "microstructures" can be on page 10, paragraph 4 of the specification, the metes and bounds of what is encompassed by the term "microstructures" is unclear since applicants do not disclose a definition and since the term does not have an art understood meaning in the context of gene enhancers/promoters, thereby rendering the scope of the claim uncertain.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-6 are rejected under 35 U.S.C. 102(b) as being anticipated by Wasserman et al. (*Journal of Molecular Biology*, 1998).

Since the language of Claims 1 and 4 invokes 35 U.S.C. 112, sixth paragraph, these claims are required to be given their broadest reasonable interpretation in light of and consistent with the written description of the invention in the application (see MPEP § 2181).

With respect to Claims 1 and 4, Wasserman et al. teaches a method performed on a computer for predicting the primary structure of a gene regulator binding site (see at least pg. 179; col. 1, paragraph 3 entitled *Software*; pg. 169, col. 2, paragraph 2; and pg. 168, col. 2, paragraph 3), comprising (a) providing a gene of interest (see at least pg. 173, col. 2, paragraph 1; and pg. 179, col. 1, paragraph 1); (b) constructing a calculation model for each of the binding sites within the enhancer or promoter, employing as parameters, loci of the regulator binding sites (see at least Pg. 169, col. 1-2; and Fig. 1); (c) computing the level of transcription of the gene with respect to the above calculation model (see at least pg. 177, col. 2, paragraph 2; and pg. 178, col. 1, bridge paragraph); (d) searching, through the use of parameter search algorithms, parameters of the calculation model so that empirically known expression of the gene is obtained (see at least pg. 171, col. 1, end of bridge paragraph; and Fig. 1 legend); and (e) predicting the identity, sequence, and arrangement (microstructures) of an enhancer/promoter (see at least Fig. 3; pg. 168, col. 2, paragraph 3; pg. 169 all; pg. 170, Col. 1; and Table 1).

With respect to Claims 2 and 5, Wasserman et al. teaches that binding energy (binding affinity) can be used as a parameter of the calculation model (see pg. 168, col. 2, middle of paragraph 1).

With respect to Claims 3 and 6, Wasserman et al. teaches a method based on the premise that where several transcription factor binding sites occur (binding sites are 'dense') in a gene regulatory region (enhancer or promoter) that a high level expression of the gene will occur, and

conversely, if no transcription factor binding sites occur (binding sites are 'sparse') that little or no expression of a gene results (see at least the abstract; and pg. 278 col. 1-2). Wasserman et al. teaches that the spacing of binding sites can vary and that cooperation of multiple factors interacting at multiple sites may be dependent on spacing constraints (see at least pg. 168, col. 1, paragraph 2; and last sentence of the abstract). Wasserman et al. further teaches that binding sites may have effects on gene expression that appear to be due to 'dense' spacing of the sites, where the sites actually do share close physical spacing (see at least Fig. 3), but also where the binding sites are spaced distantly and cooperate through remote interactions to promote expression of a gene (see at least Fig. 4; and pg. 171, col. 2, paragraph 1). Wasserman et al. also teaches that a significant number of binding sites may be identified in a region and have little effect on the expression of a gene, thus appearing to be 'sparse', because those binding sites are inactive (they are functionally independent from one another) (see at least pg. 168, col. 2, paragraph 2; and pg. 171, col. 1, paragraph 1).

Made of Record

Prior Art made of record that discloses various aspects of applicants' instant invention but was not relied upon:

US Patents: Lamb et al. (US 5707803 A), Kappan et al. (US 6303370 B1).

Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Andrew A. Kenedy whose telephone number is (571)-272-0574. The examiner can normally be reached on Monday-Friday 9:00am-5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward can be reached on (571)-272-0722. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

A.A.K.
February 9, 2004

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